Pancreatic Cancer

Five-Year Survival of Metastatic Pancreatic Carcinoma: A Study of Courage and Hope

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Median survival for patients with metastatic pancreatic adenocarcinoma is on the order of a mere 3 to 6 months. The following report of long-term survival of a patient with this devastating malignancy illustrates a highly unusual case study of hope, courage, and determination. It is the author's hope that this report might in some way prove inspirational to patients battling this demoralizing disease and provide encouragement to those physicians who treat them. The concept of weekly "metronomic" dosing of chemotherapy is also discussed, as well as targeted therapy for the treatment of pancreatic carcinoma and other cancers.

CASE REPORT

Patient A.B. is a young gentleman who presented in August 2004, at the age of 35 years, with abdominal discomfort and complaints of his food "not going down." Initial workup included a computed tomography (CT) scan of the abdomen on August 26, which showed a 9 × 8 cm soft-tissue mass at the lesser sac of the stomach, compressing the gastric body and contiguous with the pancreatic body, with a lesion in the left and right lobes of the liver consistent with metastatic disease. The patient underwent an exploratory laparotomy with biopsy of the liver lesion, cholecystectomy, and a Roux-en-Y gastrojejunostomy as a palliative bypass. Pathology revealed an adenocarcinoma, metastatic, of unknown primary, most likely from a pancreatic primary (Figure 1).

The patient was treated with gemcitabine and capecitabine from October through November, suffering significant side effects and evidence of disease progression. He was then switched to gemcitabine and docetaxel on December 12. A CT scan performed on January 10, 2005, showed further disease progression (Figure 2). By this time, the patient was severely ill and debilitated, and hospice was suggested.

The patient and his wife visited our clinic on January 28. He was confined to a wheelchair at the time and had an Eastern Cooperative Oncology Group (ECOG) score of 4. He was informed that his prognosis was indeed quite poor, especially since no standard treatment existed for metastatic pancreatic carcinoma after failing a gemcitabine-based regimen. Nevertheless, his desire was to continue treatment. Because of his young age and our experience with "metronomic" chemotherapy dosing, he was offered a salvage regimen consisting of weekly metronomic dosing of paclitaxel 60 mg/m^2, oxaliplatin 50 mg/m^2, leucovorin 40 mg, and 5-fluorouracil (5-FU) 425 mg/m^2 (POLF), which he started on January 31. To prevent neuropathy, calcium and magnesium, as well as glutathione, were given intravenously; glutamine was administered orally.[1–5]

The patient, who was receiving care at a nursing home, required paramedic transportation on a stretcher to and from the clinic for his treatment sessions. Many of his caregivers felt at the time that treatment was futile and encouraged him to accept hospice care. Despite the odds, however, he insisted on continuing treatment. The patient tolerated the treatment extremely well, with virtually no side effects, receiving 4 weeks of the POLF regimen before his chemotherapy had to be held because of low blood cell counts, at which time he received a dose of cetuximab in the hope that the epidermal growth factor receptor (EGFR) inhibitor might contribute to control of his disease. After receiving cetuximab, the patient developed a moderate rash, a common side effect of HER1/EGFR-targeted agents.

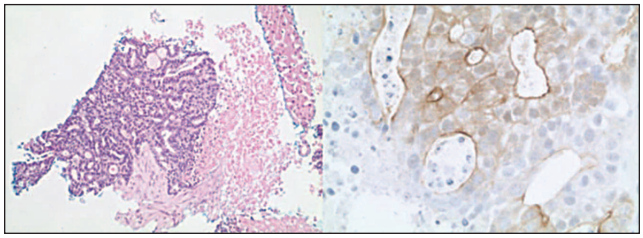

Figure 1. Original biopsy specimens of the metastatic liver lesion. Analysis revealed metastatic adenocarcinoma, most likely from a pancreatic primary.

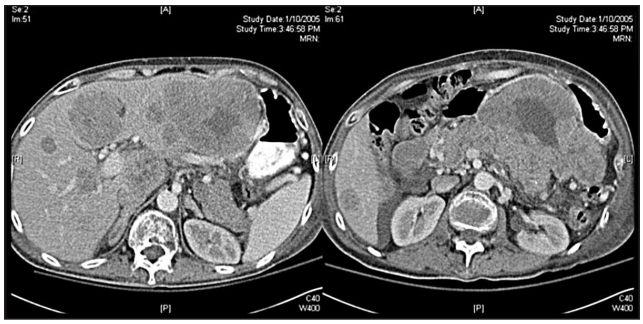

Figure 2. Baseline computed tomography (CT) images from January 2005 showing a large mass at the tail of the pancreas and extensive liver metastases.

Chemotherapy with POLF continued, along with intermittent cetuximab. Remarkably, a CT scan of the patient's liver performed on April 27 showed a decrease in tumor size from 10 cm to 5 cm. His CA 19.9 had also decreased from a pretreatment level of 489 U/mL to a normal 18 U/mL. The patient continued to receive chemotherapy as the size of tumors in both his liver and pancreas con-

tinued to decrease (Figure 3). As his performance status improved, he was able to begin physical therapy. With encouragement and support from his family, Mr. A.B. continued to improve clinically.

Throughout the first 4 months of treatment (during which time he was hospitalized twice), the patient continued to require transportation on a stretcher. Subsequently, he was able to be transported in a wheelchair. As he continued to improve, he was eventually able to ambulate with a walker, then a cane; ultimately, the patient was able to walk without any assistance. He continued treatment for 52 weeks with the POLF chemotherapy and intermittent cetuximab. Of note, the patient developed only mild neuropathy, which resolved off treatment.

On March 28, 2006, the patient's case was presented to the Gastrointestinal Tumor Board at Swedish Hospital in Seattle, where his pathology reports and scans were reviewed. Because of his unusually long survival, doubts arose as to the original diagnosis of metastatic pancreatic adenocarcinoma. The diagnosis, however, was confirmed. Follow-up positron emission tomography (PET)/CT scans showed only a 2-cm lesion remaining in the liver, and no residual disease in the pancreas, nor any other evidence of disease. The patient was evaluated as a possible candidate for resection of the remaining lesion in the liver. After careful deliberation — which included consultations with surgeons in the United States and Europe — it was decided that (1) the risk of significant morbidity and mortality was too high, given this patient's previous surgery (which included accidental laceration of an artery with need for immediate repair), and (2) the potential benefit of surgery for his metastatic disease was deemed questionable.

Further chemotherapy was recommended, but it remained to be decided which regimen would be most appropriate. Ultimately, the patient was switched to weekly paclitaxel/irinotecan/oxaliplatin on May 9, with intermittent cetuximab until August 28. Subsequently he was treated with erlotinib and low-dose interferon, weekly paclitaxel and gemcitabine, and then again with weekly POLF from October 15, 2007, to February 4, 2008. On February 5, a PET/CT scan showed a small lesion in the pancreas and a 1.8-cm lesion in the central part of the liver, but without evidence of hypermetabolic activity (Figure 4). Follow-up PET/CT scan on August 5, however, showed two hypermetabolic lesions in the tail of the pancreas measuring 2.8 × 1.3 cm and 1.0 × 1.0 cm.

The patient's case was again presented to the Gastrointestinal Tumor Board at Swedish Hospital on August 14, where his scans were re-examined, and more importantly, his biopsy specimens were reviewed once more by another pathologist, who again confirmed the diagnosis of adenocarcinoma of the pancreas, but with a few cells staining positive for a neuroendocrine tumor. The recommendation of the Tumor Board was to rebiopsy one of the lesions in the pancreas to reconfirm the diagnosis of a metastatic pancreatic adenocarcinoma.

The patient underwent endoscopic ultrasound with a transgastric biopsy of one of the lesions at the tail of the pancreas on August 22. Histopathologic analysis again revealed an adenocarcinoma with minimal staining for synaptophysin, excluding a predominantly neuroendocrine differentiated neoplasm and reconfirming the original diagnosis of pancreatic adenocarcinoma (Figure 5). In addition, KRAS testing was performed, which demonstrated the presence of the wild-type (or nonmutated) gene in the specimen. The patient resumed further treatment with weekly paclitaxel/cisplatin/irinotecan plus cetuximab, with good disease control.

Five years out from his diagnosis of metastatic pancreatic adenocarcinoma, Mr. A.B. is doing extremely well — his current ECOG score is 0, he has returned to work, and he recently completed the "Seattle to Portland" bicycle marathon, a distance of 175 miles.

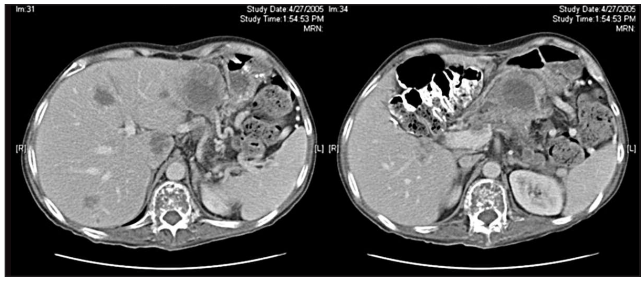

Figure 3. CT scans performed in April 2006 show decreased tumor volume in liver (left) and pancreas (right).

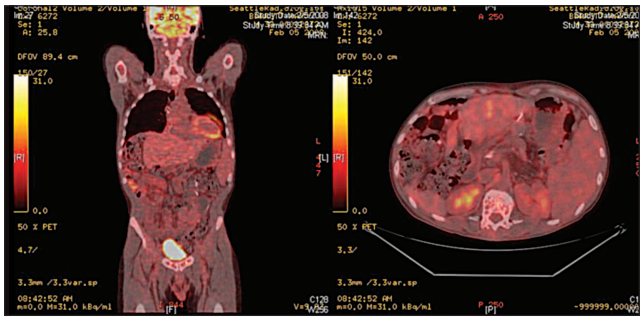

Figure 4. February 2008 PET/CT scan showed a small lesion in the pancreas and a 1.8-cm lesion in the central part of the liver, but no evidence of hypermetabolic activity.

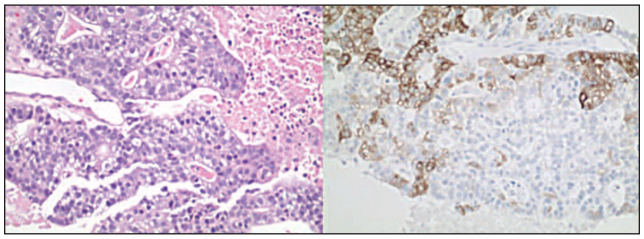

Figure 5. Histopathologic analysis of the pancreatic lesion specimens obtained in August 2008 reconfirmed the original diagnosis of pancreatic adenocarcinoma.

DISCUSSION

The rationale behind treatment with a weekly "metronomic" dosing of POLF is that, though there is no standard chemotherapy beyond first-line chemotherapy with a gemcitabine-based regimen, both oxaliplatin and leucovorin/5-FU have shown activity in this disease.[6,7] A recently reported phase III trial also supports the use of these agents.[8] Dr. Margaret Tempero from the University of California, San Francisco, as spokesperson for the National Comprehensive Cancer Network, has also recommended oxaliplatin and a fluorinated pyrimidine as second-line treatment for metastatic pancreatic carcinoma after failure of a gemcitabine-based chemotherapy.[9] Paclitaxel, especially when administered on a weekly metronomic schedule, may also have activity in pancreatic cancer,[10] with encouraging results recently shown with nab-

paclitaxel and cationic liposomal paclitaxel (EndoTAG-1) in combination with gemcitabine.[11,12]

A more steady, metronomic dosing can result in fewer side effects, leading to better tolerability, but also increased efficacy due to the increased dose density and dose intensity that can be achieved compared to "traditional" chemotherapy.[13] The importance of dose density and dose intensity in achieving chemotherapy efficacy is well known.[14–16] In addition, the metronomic dosing of chemotherapy may have antiangiogenic properties due to its effects on endothelial cells,[17–20] especially with paclitaxel[21,22] and perhaps also with 5-FU.[23,24] The importance of inhibiting or reversing angiogenesis in cancer control is clearly established.[25,26] Recent results of weekly metronomic dosing have shown paclitaxel to be more effective than the previous standard doses of this agent given every 3 weeks in the neoadjuvant,[27] adjuvant,[28] and metastatic[29] settings in breast cancer, with a similar benefit seen in ovarian cancer.[30]

Studies with the antiangiogenic agent bevacizumab, a monoclonal anti–vascular endothelial growth factor antibody, indicate that antiangiogenic agents might lower tumor interstitial pressure, which could increase chemotherapy delivery to the tumor bed and thus improve efficacy.[31,32] Weekly paclitaxel may therefore facilitate increased efficacy of the other chemotherapy agents, such as oxaliplatin and 5-FU, by allowing the agents to reach the tumor better and yet cause fewer side effects systemically, since lower doses of chemotherapy need to be used to attain equal or higher concentrations of the chemotherapy in the tumor bed.

The seeming lack of activity of various chemotherapies and other therapeutic agents, including targeted therapies, and even cells of the immune system in various cancers, may not be due to their inability to kill or inhibit a cancer in the clinical setting, but rather due to their inability to reach the tumor cells in vivo, because of the development of aberrant, diverting blood vessels with tumor angiogenesis. This would explain the interesting and clinically significant finding that in vitro chemotherapy resistance tests appear to correlate better with lack of activity of chemotherapy agents in the clinical setting than in vitro chemotherapy sensitivity tests correlate with the presence of clinical activity.[33] Lack of efficacy of many agents against cancer may therefore be due simply to lack of accessibility to the tumor cells. Blocking angiogenesis by adding antiangiogenic agents such as bevacizumab (and possibly weekly paclitaxel) may eliminate this problem and thus optimize the efficacy of various chemotherapies.[34]

The concept of adding an antiangiogenic agent to chemotherapy to make chemotherapy more effective may also apply to other agents, including targeted therapies. For example, the recent results of the ATLAS and BeTa trials in non–small-cell lung cancer suggest the benefits of combining bevacizumab with the EGFR tyrosine kinase inhibitor erlotinib.[35,36]

Data on the POLF regimen for metastatic pancreatic adenocarcinoma have previously been reported.[37–40] A phase II clinical trial with the POLF regimen is currently under way (clinicaltrials.gov, identifier #NCT00323583), but accrual has been slow. This concept of using metronomic dosing of chemotherapy, especially with weekly paclitaxel, may apply to other chemotherapy regimens as well.[41]

Of note is that the patient's pancreatic adenocarcinoma showed no KRAS mutation. Recent work in metastatic colon cancer has shown that only colon cancers that have nonmutated KRAS respond to cetuximab and other therapies directed against the epidermal growth factor receptor.[42,43] A recent trial looking at the addition of cetuximab to gemcitabine in the treatment of metastatic pancreatic carcinoma showed no survival benefit with the addition of cetuximab.[44] However, 90%–95% of pancreatic adenocarcinomas have a mutated KRAS,[45–47] which may have resulted in these negative findings. It is therefore possible that cetuximab may have efficacy in the remaining 5%–10% of patients with pancreatic carcinomas that have wild-type KRAS, including our patient, contributing to his unusually long survival. A clinical trial to test this possibility would be useful.

This report of a patient with metastatic pancreatic carcinoma who responded extremely well to treatment is, of course, a highly unusual case. As we hope to see him continue to do well over time, we hold on to the hope that we will be able to make substantial progress in this devastating disease — indeed all cancers — with new, innovative therapies[48] and with the help of such brave, determined, and unrelenting patients as this extraordinary gentleman who remained optimistic despite an extremely poor prognosis and dismal expectations.[49] The efficacy and yet excellent tolerability of metronomic dosing of POLF and possibly other chemotherapies for metastatic pancreatic adenocarcinoma, justly recognized as one of the worst, most aggressive human cancers, suggest a role for this type of treatment for other cancers, and in other settings[28,29] We encourage further research on this concept of metronomic dosing of chemotherapy and other agents, which may be able to improve efficacy and yet minimize side effects, which is the ultimate goal for all therapeutic interventions.

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Disclosure of Potential Conflicts of Interest

Dr. Chue indicated no potential conflicts of interest.